SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Propofol 2% (20 mg/ml) emulsion for injection or infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml emulsion for injection or infusion contains

Propofol	20	mg
One vial of 50 ml contains	1000	mg propofol

Excipients with known effect
1 ml emulsion for injection or infusion contains
Soya-bean oil, refined 50 mg

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Emulsion for injection or infusion
White milky oil-in-water emulsion

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Propofol 2% (20 mg/ml) is a short-acting intravenous general anaesthetic for

- induction and maintenance of general anaesthesia in adults and children > 3 years
- sedation of ventilated patients > 16 years of age in the intensive care unit
- sedation for diagnostic and surgical procedures, alone or in combination with local or regional anaesthesia in adults and children > 3 years.

4.2 Posology and method of administration

General instructions

Propofol must only be given in hospitals or adequately equipped day therapy units by physicians trained in anaesthesia or in the care of patients in intensive care. Circulatory and respiratory functions should be constantly monitored (e.g. ECG, pulse oximeter) and facilities for maintenance of patent airways, artificial ventilation, and other resuscitation facilities should be immediately available at all times. For sedation during surgical or diagnostic procedures Propofol should not be given by the same person that carries out the surgical or diagnostic procedure.

Supplementary analgesic medicinal products are generally required in addition to Propofol.

Posology

Propofol is given intravenously. The dosage is adjusted individually according to the patient's response.

- *General anaesthesia in adults*

Induction of anaesthesia:

For induction of anaesthesia Propofol should be titrated (20-40 mg propofol every 10 seconds) against the patient's response until the clinical signs show the onset of anaesthesia. Most adult patients younger than 55 years are likely to require 1.5 to 2.5 mg/kg body weight.
In patients over this age and in patients of ASA grades III and IV, especially those with impaired cardiac function, the dosage requirements will be less and the total dose of Propofol may be reduced to a minimum of 1 mg/kg body weight. In these patients lower rates of administration should be applied (approximately 1 ml corresponding to 20 mg every 10 seconds).

Maintenance of anaesthesia:

Anaesthesia is maintained by administering Propofol by continuous infusion. The dosage requirements usually are in the range of 4-12 mg/kg body weight/h.
In elderly patients, in patients of poor general condition, in patients of ASA grades III and IV, in hypovolaemic patients and patients with hypoproteinaemia the dosage may have to be reduced further depending on the severity of the patient´s condition and on the performed anaesthetic technique.

- *General anaesthesia in children over 3 years of age*

Induction of anaesthesia:

For induction of anaesthesia Propofol should be slowly titrated against the patient's response until the clinical signs show the onset of anaesthesia. The dosage should be adjusted according to age and/or body weight.
Most patients over 8 years of age require approximately 2.5 mg/kg body weight of propofol for induction of anaesthesia.

Maintenance of general anaesthesia:

Anaesthesia can be maintained by administering Propofol by infusion to maintain the depth of anaesthesia required. The required rate of administration varies considerably

between patients but rates in the region of 9-15 mg/kg/h usually achieve satisfactory anaesthesia.

For ASA III and IV patients lower doses are recommended (see also section 4.4)

- *Sedation of ventilated patients in the intensive care unit*

For sedation during intensive care, it is advised that Propofol should be administered by continuous infusion. The infusion rate should be determined by the desired depth of sedation. In most patients sufficient sedation can be obtained with a dosage of 0.3-4.0 mg of propofol per kg body weight per hour (see section 4.4).

Propofol is not indicated for sedation of patients of 16 years or younger in intensive care (see section 4.3). Administration of propofol by Target Controlled Infusion (TCI) system is not advised for sedation in the intensive care unit.

- *Sedation for diagnostic and surgical procedures in adults*

To provide sedation during surgical and diagnostic procedures, doses and administration rates should be adjusted according to the clinical response. Most patients will require 0.5-1 mg/kg body weight over 1 to 5 minutes for onset of sedation. Maintenance of sedation may be accomplished by titrating Propofol infusion to the desired level of sedation. Most patients will require 1.5-4.5 mg/kg body weight/h.
In patients older than 55 years and in patients of ASA grades III and IV lower doses of Propofol may be required and the rate of administration may need to be reduced.

According to required dose, alternatively Propofol 1% (10 mg/ml) may be used.

- *Sedation for diagnostic and surgical procedures in children over 3 years of age*

Doses and administration rates should be adjusted according to the required depth of sedation and the clinical response. Most paediatric patients require 1-2 mg/kg body weight of propofol for onset of sedation. Maintenance of sedation may be accomplished by titrating of propofol infusion to the desired level of sedation. Most patients require 1.5-9 mg/kg/h of propofol.

In ASA III and IV patients lower doses may be required.

Method and duration of administration

- *Method of administration*

Intravenous use

Propofol is administered undiluted by injection or continuous infusion. Containers should be shaken before use.

Before use, the surface of the rubber stopper of the vial should be cleaned with medicinal alcohol (spray or swabs). After use, tapped containers must be discarded.

Propofol contains no antimicrobial preservatives and supports growth of microorganisms. Therefore, Propofol is to be drawn up aseptically into a sterile syringe or an infusion set immediately after breaking the vial seal. Administration

must commence without delay. Asepsis must be maintained for both Propofol and the infusion equipment throughout the entire period of administration.

Any medicinal products or fluids added to a running Propofol 2% (20 mg/ml) infusion must be administered close to the cannula site. If infusion sets with filters are to be used, these must be lipid-permeable.

The contents of one vial of Propofol and any syringe containing Propofol are for **single use** in **one** patient. Any portion of the contents remaining after use must be discarded.

For administration of Propofol by continuous infusion, it is recommended that burettes, drop counters, syringe pumps or volumetric infusion pumps should always be used to control the infusion rates. As established for the parenteral administration of all kinds of fat emulsions, the duration of continuous infusion of Propofol from **one** infusion system must not exceed 12 hours. The infusion line and the reservoir of Propofol must be discarded and replaced after 12 hours at the latest. Any portion of Propofol remaining after the end of infusion or after replacement of the infusion system must be discarded.

In order to reduce pain on initial injection of Propofol for induction of general anaesthesia, lidocaine may be injected immediately prior to the injection of Propofol.

Before giving the muscle relaxants atracurium or mivacurium subsequent to Propofol through the same intravenous line, the line should be rinsed prior to administration.

Propofol may also be used by Target Controlled Infusion. Due to the different algorithms available on the market for dosage recommendations please refer to the instructions for use leaflet of the device manufacturer.

- *Duration of administration*

Propofol can be administered for a maximum period of 7 days.

4.3 Contraindications

Hypersensitivity to the active substance, soya, peanut or to any of the excipients listed in section 6.1.

Propofol must not be used in patients of 16 years of age or younger for sedation for intensive care. Safety and efficacy for these age groups have not been demonstrated (see section 4.4).

4.4 Special warnings and precautions for use

Propofol should be given by those trained in anaesthesia (or, where appropriate, doctors trained in the care of patients in Intensive Care).

Patients should be constantly monitored and facilities for maintenance of a patent airway, artificial ventilation, oxygen enrichment and other resuscitative facilities should be readily available at all times. Propofol should not be administered by the person conducting the diagnostic or surgical procedure.

The abuse of and dependence on propofol, predominantly by health care professionals, have been reported. As with other general anaesthetics, the administration of propofol without airway care may result in fatal respiratory complications.

When propofol is administered for conscious sedation, for surgical and diagnostic procedures, patients should be continually monitored for early signs of hypotension, airway obstruction and oxygen desaturation.

As with other sedative agents, when propofol is used for sedation during operative procedures, involuntary patient movements may occur. During procedures requiring immobility these movements may be hazardous to the operative site.

An adequate period is needed prior to discharge of the patient to ensure full recovery after use of propofol. Very rarely the use of propofol may be associated with the development of a period of post-operative unconsciousness, which may be accompanied by an increase in muscle tone. This may or may not be preceded by a period of wakefulness. Although recovery is spontaneous, appropriate care of an unconscious patient should be administered.

Propofol induced impairment is not generally detectable beyond 12 hours. The effects of propofol, the procedure, concomitant medications, the age and the condition of the patient should be considered when advising patients on:

- The advisability of being accompanied on leaving the place of administration
- The timing of recommencement of skilled or hazardous tasks such as driving
- The use of other agents that may sedate (e.g. benzodiazepines, opiates, alcohol).

As with other intravenous anaesthetic agents, caution should be applied in patients with cardiac, respiratory, renal or hepatic impairment or in hypovolaemic or debilitated patients (see also section 4.2).

Propofol clearance is blood flow dependent, therefore, concomitant medication that reduces cardiac output will also reduce propofol clearance.

Propofol lacks vagolytic activity and has been associated with reports of bradycardia (occasionally profound) and also asystole. The intravenous administration of an anticholinergic agent before induction or during maintenance of anaesthesia should be considered, especially in situations where vagal tone is likely to predominate or when propofol is used in conjunction with other agents likely to cause bradycardia.

When propofol is administered to an epileptic patient, there may be a risk of convulsion.
Appropriate care should be applied in patients with disorders of fat metabolism and in other conditions where lipid emulsions must be used cautiously.

Patients with hypoproteinaemia might have a higher risk to obtain adverse events based on a higher fraction of unbound propofol. Dose reduction in these patients is recommended (see also section 4.2).

Paediatric population

The use of propofol is not recommended in newborn infants as this patient population has not been fully investigated. Pharmacokinetic data (see section 5.2) indicate that clearance is considerably reduced in neonates and has a very high inter-individual variability. Relative overdose could occur on administering doses recommended for older children and result in severe cardiovascular depression.

Propofol 2% (20 mg/ml) is not recommended for use in children < 3 years of age due to difficulty in titrating small volumes.

Propofol must not be used in patients of 16 years of age or younger for sedation for intensive care as the safety and efficacy of propofol for sedation in this age group have not been demonstrated (see section 4.3).

Advisory statements concerning Intensive Care Unit management

Use of propofol for ICU sedation has been associated with a constellation of metabolic disturbances and organ system failures that may result in death. Reports have been received of combinations of the following: Metabolic acidosis, Rhabdomyolysis, Hyperkalaemia, Hepatomegaly, Renal failure, Hyperlipidaemia, Cardiac arrhythmia, Brugada-type ECG (elevated ST-segment and coved T-wave) and rapidly progressive Cardiac failure usually unresponsive to inotropic supportive treatment. Combinations of these events have been referred to as the **Propofol infusion syndrome**. These events were mostly seen in patients with serious head injuries and children with respiratory tract infections who received dosages in excess of those advised in adults for sedation in the intensive care unit.

The following appear to be the major risk factors for the development of these events: decreased oxygen delivery to tissues; serious neurological injury and/or sepsis; high dosages of one or more of the following pharmacological agents – vasoconstrictors, steroids, inotropes and/or propofol (usually at dose rates greater than 4 mg/kg/h for more than 48 hours).

Prescribers should be alert to these events in patients with the above risk factors and immediately discontinue propofol when the above signs develop. All sedative and therapeutic agents used in the intensive care unit (ICU), should be titrated to maintain optimal oxygen delivery and haemodynamic parameters. Patients with raised intra-cranial pressure (ICP) should be given appropriate treatment to support the cerebral perfusion pressure during these treatment modifications. Treating physicians are reminded if possible not to exceed the dosage of 4 mg/kg/h.

Appropriate care should be applied in patients with disorders of fat metabolism and in other conditions where lipid emulsions must be used cautiously.

It is recommended that blood lipid levels should be monitored if propofol is administered to patients thought to be at particular risk of fat overload. Administration of propofol should be adjusted appropriately if the monitoring indicates that fat is being inadequately cleared from the body. If the patient is receiving other intravenous lipid concurrently, a reduction in quantity should be made in order to take account of the amount of lipid infused as part of the propofol formulation; 1.0 ml of Propofol contains 0.1 g of fat.

Additional precautions

Caution should be taken when treating patients with mitochondrial disease. These patients may be susceptible to exacerbations of their disorder when undergoing anaesthesia, surgery and ICU care. Maintenance of normothermia, provision of

carbohydrates and good hydration are recommended for such patients. The early presentations of mitochondrial disease exacerbation and of the 'propofol infusion syndrome' may be similar.

Propofol contains no antimicrobial preservatives and supports growth of micro-organisms.
When propofol is to be aspirated, it must be drawn aseptically into a sterile syringe or giving set immediately after opening the ampoule or breaking the vial seal. Administration must commence without delay. Asepsis must be maintained for both propofol and infusion equipment throughout the infusion period.

Propofol and any syringe containing propofol are for single use in an individual patient. In accordance with established guidelines for other lipid emulsions, a single infusion of propofol must not exceed 12 hours. At the end of the procedure or at 12 hours, whichever is the sooner, both the reservoir of propofol and the infusion line must be discarded and replaced as appropriate.

This medicinal product contains less than 1 mmol sodium (23 mg) per 100 ml, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Propofol has been used in association with spinal and epidural anaesthesia and with commonly used premedicants, neuromuscular blocking medicinal products, inhalational medicinal products and analgesic medicinal products; no pharmacological incompatibility has been encountered. Lower doses of propofol may be required where general anaesthesia or sedation is used as an adjunct to regional anaesthetic techniques. The concurrent administration of other CNS depressants such as pre-medication medicinal products, inhalation medicinal products, analgesic medicinal products may add to the sedative, anaesthetic and cardiorespiratory depressant effects of propofol. Profound hypotension has been reported following anaesthetic induction with propofol in patients treated with rifampicin.

A need for lower propofol doses has been observed in patients taking valproate. When used concomitantly, a dose reduction of propofol may be considered.

4.6 Fertility, pregnancy and lactation

Pregnancy
The safety of propofol during pregnancy has not been established.
Studies in animals have shown reproductive toxicity (see section 5.3).
Propofol should not be given to pregnant women except when absolutely necessary.
Propofol crosses the placenta and can cause neonatal depression. Propofol can, however, be used during an induced abortion.

Breast-feeding
Studies of breast-feeding mothers showed that small quantities of propofol are excreted in human milk. Women should therefore not breastfeed for 24 hours after administration of propofol. Milk produced during this period should be discarded.

Fertility
No data available.

4.7 Effects on ability to drive and use machines

Patients should be advised that performance at skilled tasks, such as driving and operating machinery, may be impaired for some time after use of propofol.

Propofol induced impairment is not generally detectable beyond 12 hours (please see section 4.4).

4.8 Undesirable effects

Induction and maintenance of anaesthesia or sedation with propofol is generally smooth with minimal evidence of excitation. The most commonly reported ADRs are pharmacologically predictable side effects of an anaesthetic/sedative agent, such as hypotension. The nature, severity and incidence of adverse events observed in patients receiving propofol may be related to the condition of the recipients and the operative or therapeutic procedures being undertaken.

Table of Adverse Drug Reactions

System Organ Class	Frequency	Undesirable Effects
Immune system disorders:	Very rare (< 1/10 000)	Anaphylaxis up to anaphylactic shock – may include angioedema, bronchospasm, erythema and hypotension
Metabolism and nutritional disorders:	Frequency not known (9)	Metabolic acidosis (5), hyperkalaemia (5), hyperlipidaemia (5)
Psychiatric disorders:	Very rare (< 1/10 000)	Sexual disinhibition
	Frequency not known (9)	Euphoric mood, drug abuse and drug dependence (8)
Nervous system disorders:	Common (≥ 1/100, < 1/10)	Headache during recovery phase
	Rare (≥ 1/10 000, < 1/1000)	Epileptiform movements, including convulsions and opisthotonus during induction, maintenance and recovery
	Very rare (< 1/10 000)	Postoperative unconsciousness
	Frequency not known (9)	Involuntary movements
Cardiac disorders:	Common (≥ 1/100, < 1/10)	Bradycardia (1)

	Very rare (< 1/10 000)	Pulmonary oedema
	Frequency not known (9)	Cardiac arrhythmia (5), cardiac arrest, cardiac failure (5), (7)
Vascular disorders:	Common (≥ 1/100, < 1/10)	Hypotension (2)
Respiratory, thoracic and mediastinal disorders:	Common (≥ 1/100, < 1/10)	Transient apnoea during induction
	Frequency not known (9)	Respiratory depression (dose-dependent)
Gastrointestinal disorders:	Common (≥ 1/100, < 1/10)	Nausea and vomiting during recovery phase
	Very rare (< 1/10 000)	Pancreatitis
Hepatobiliary disorders:	Frequency not known (9)	Hepatomegaly (5), hepatitis (12), acute hepatic failure (12)
Musculoskeletal and connective tissue disorders:	Frequency not known (9)	Rhabdomyolysis (3), (5)
Reproductive system and breast disorders:	Frequency not known (9)	Priapism
Renal and urinary disorders:	Very rare (< 1/10 000)	Discolouration of urine following prolonged administration
	Frequency not known (9)	Renal failure (5)
General disorders and administration site conditions:	Very common (≥ 1/10)	Local pain on induction (4)
	Uncommon (≥ 1/1000, < 1/100)	Injection site thrombosis and injection site phlebitis
	Very rare (< 1/10 000)	Tissue necrosis (10) following accidental extravascular administration (11)
	Frequency not known (9)	Local pain, swelling and inflammation, following accidental extravascular administration (11)
Investigations:	Frequency not known (9)	Brugada type ECG (5), (6)
Injury, poisoning and procedural complications:	Very rare (< 1/10 000)	Postoperative fever

(1) Serious bradycardias are rare. There have been isolated reports of progression to asystole.

(2) Occasionally, hypotension may require use of intravenous fluids and reduction of the administration rate of propofol.

(3) Very rare reports of rhabdomyolysis have been received where propofol has been given at doses greater than 4 mg/kg/hr for ICU sedation.
(4) May be minimised by using the larger veins of the forearm and antecubital fossa. With Propofol local pain can also be minimised by the co-administration of lidocaine.
(5) Combinations of these events, reported as "Propofol infusion syndrome", may be seen in seriously ill patients who often have multiple risk factors for the development of the events, see section 4.4.
(6) Brugada-type ECG – elevated ST-segment and coved T-wave in ECG.
(7) Rapidly progressive cardiac failure (in some cases with fatal outcome) in adults. The cardiac failure in such cases was usually unresponsive to inotropic supportive treatment.
(8) Abuse of and drug dependence on propofol, predominantly by health care professionals.
(9) Not known as it cannot be estimated from the available clinical trial data.
(10) Necrosis has been reported where tissue viability has been impaired.
(11) Treatment is symptomatic and may include immobilisation and, if possible, elevation of affected limb, cooling, close observation, consultation of surgeon if necessary.
(12) After both long- and short-term treatment and in patients without underlying risk factors.

4.9 Overdose

Symptoms
Accidental overdosage is likely to cause cardiorespiratory depression.

Treatment
Respiratory depression should be treated by artificial ventilation with oxygen. Cardiovascular depression may require lowering of the patient's head and, if severe, use of plasma expanders and pressor agents.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other general anaesthetics, ATC-code N01AX10.

Mechanism of action, pharmacodynamic effect
After intravenous injection of Propofol, onset of the hypnotic effect is rapid. Depending on the rate of injection, the time to induction of anaesthesia is between 30 and 40 seconds.

Patients recover consciousness rapidly.

Bradycardia and hypotension occasionally occur during induction of anaesthesia probably due to the lack of vagolytic activity. The cardio-circulatory situation usually normalises during maintenance of anaesthesia.

Paediatric population
Limited studies on the duration of propofol based anaesthesia in children indicate safety and efficacy is unchanged up to duration of 4 hours. Literature evidence of use in children documents use for prolonged procedures without changes in safety or efficacy.

5.2 Pharmacokinetic properties

Absorption
After intravenous administration about 98% of propofol is bound to plasma protein.

Distribution
After intravenous bolus administration the initial blood level of propofol declines rapidly due to rapid distribution into different compartments (α-phase). The distribution half-life has been calculated as 2-4 minutes.

During elimination the decline of blood levels is slower. The elimination half-life during the ß-phase is in the range of 30 to 60 minutes. Subsequently a third deep compartment becomes apparent, representing the re-distribution of propofol from weakly perfused tissue.

The central volume of distribution is in the range of 0.2-0.79 l/kg body weight, the steady-state volume of distribution in the range of 1.8-5.3 l/kg body weight.

Biotransformation
Propofol is mainly metabolised in the liver to form glucuronides of propofol and glucuronides and sulphate conjugates of its corresponding quinol. All metabolites are inactive.

Elimination
Propofol is rapidly cleared from the body (total clearance approx. 2 l/min). Clearance occurs by metabolism, mainly in the liver, where it is blood flow dependent. Clearance is higher in paediatric patients compared with adults. About 88% of an administered dose is excreted in the form of metabolites in urine. Only 0.3% is excreted unchanged in the urine.

Paediatric population
After a single dose of 3 mg/kg intravenously, propofol clearance/kg body weight increased with age as follows: Median clearance was considerably lower in neonates < 1 month old (n = 25) (20 ml/kg/min) compared to older children (n = 36, age range 4 months – 7 years). Additionally, inter-individual variability was considerable in neonates (range 3.7-78 ml/kg/min). Due to this limited trial data that indicates a large variability, no dose recommendations can be given for this age group.

Median propofol clearance in older aged children after a single 3 mg/kg bolus was 37.5 ml/min/kg (4-24 months) (n = 8), 38.7 ml/min/kg (11-43 months) (n = 6), 48 ml/min/kg (1-3 years) (n = 12), 28.2 ml/min/kg (4-7 years) (n = 10) as compared with 23.6 ml/min/kg in adults (n = 6).

5.3 Preclinical safety data

Preclinical data reveal no specific hazard for humans based on conventional studies on repeated dose toxicity or genotoxicity. Carcinogenicity studies have not been conducted.

Published studies in animals (including primates) at doses resulting in light to moderate anaesthesia demonstrate that the use of anaesthetic agents during the period of rapid brain growth or synaptogenesis results in cell loss in the developing brain that can be associated with prolonged cognitive deficiencies. The clinical significance of these nonclinical findings is not known. Teratogenic effects have not been observed.

In local tolerance studies, intramuscular injection resulted in tissue damage around the injection site.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Soya-bean oil, refined,
Medium-chain triglycerides,
Glycerol,
Egg phospholipids for injection,
Sodium oleate,
Water for injections.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

2 years.

After first opening:
To be used immediately.

6.4 Special precautions for storage

Do not store above 25 °C.
Do not freeze.

6.5 Nature and contents of container

The product is supplied in

- vials of colourless glass (type II Ph. Eur.) sealed with bromobutyl rubber stoppers and aluminium caps, containing 50 ml of emulsion. It is available in packs of 1 x 50 ml, 10 x 50 ml

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

Containers should be shaken before use.

For single use only. Any portion of contents remaining after first use must be discarded, see sections 4.2 and 4.4.

If two layers can be seen after shaking, the medicinal product should not be used.

Propofol must not be mixed with other solutions for injection or infusion. However, co-administration of Propofol together with glucose 50 mg/ml (5% w/v) solution for infusion or sodium chloride 9 mg/ml (0.9% w/v) solution for infusion, or sodium chloride 1.8 mg/ml (0.18% w/v) and glucose 40 mg/ml (4% w/v) solution via a Y-connector close to the injection site is possible.

7 MARKETING AUTHORISATION HOLDER

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